COPY

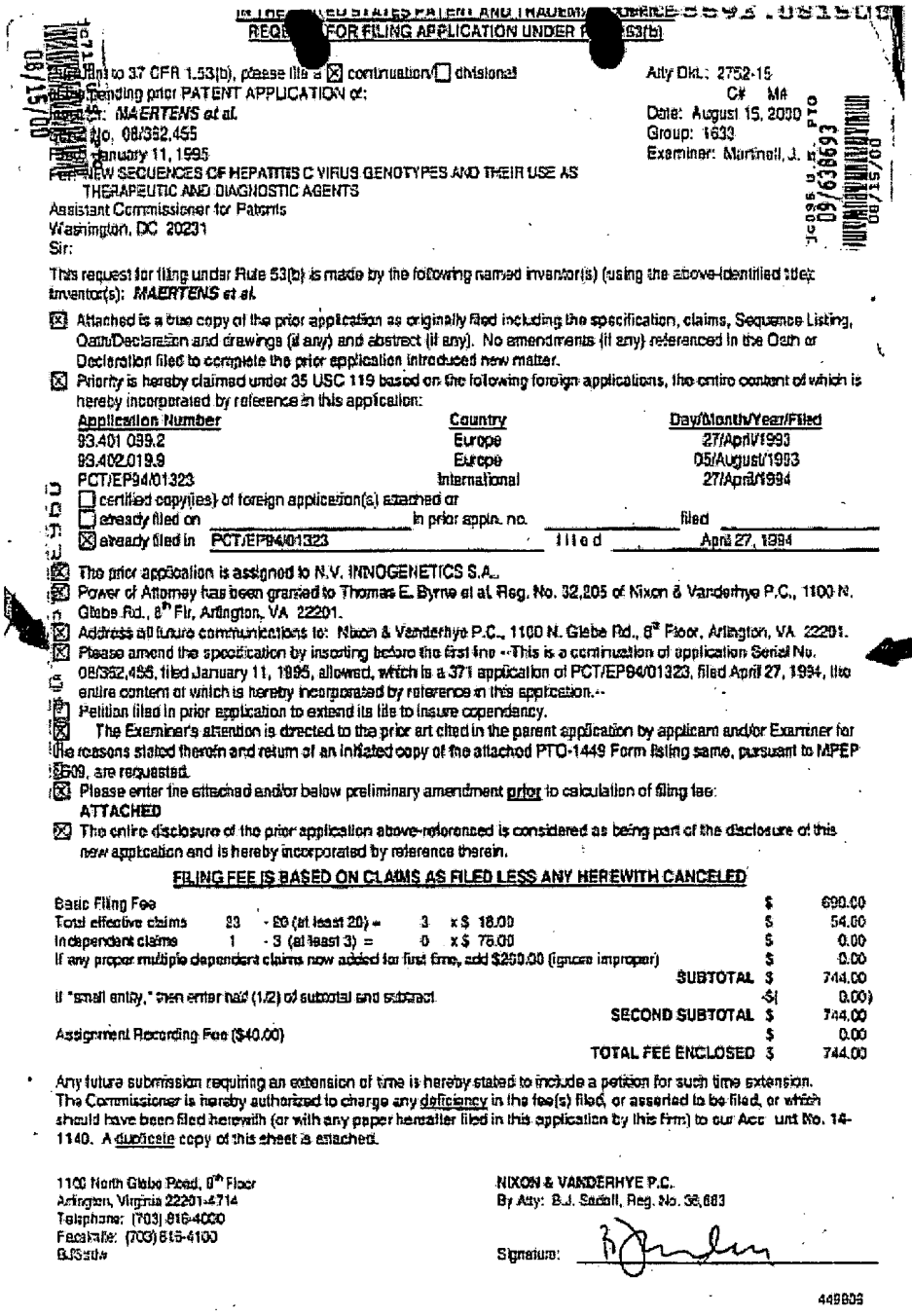
REMARKS

Reconsideration is requested.

The specification has been amended to be consistent with the related, recently-issued application Serial No. 09/878,281, now U.S. Patent No. 6,762,024, which was examined by the examiner of the present application. The amendments to the specification of the related application to include sequence identifiers were require in an Office Action dated April 25, 2003.

The specification has been amended in the first paragraph, to include a cross-reference to the parent applications. The applicants requested that this same paragraph be added as an Amendment stated on the applicants Transmittal of the new application on August 15, 2000. The following is a copy of the Transmittal of August 15, 2000 retrieved from the USPTO PAIR database by the undersigned wherein previously-requested amendment has been indicated by Arrows by the undersigned.

COPY



IN THE [redacted] STATES PATENT AND TRADEMARK [redacted]

REQUEST FOR FILING APPLICATION UNDER [redacted] 53(b)

Pursuant to 37 CFR 1.53(b), please file a ☒ continuation/☐ divisional of the pending prior PATENT APPLICATION of:

Atty Dkt.: 2752-15
C# MA
Date: August 15, 2000
Group: 1633
Examiner: Martinell, J. [redacted]

Inventor: *MAERTENS et al.*
Ser. No. 08/362,455
Filed: January 11, 1995
For: NEW SEQUENCES OF HEPATITIS C VIRUS GENOTYPES AND THEIR USE AS THERAPEUTIC AND DIAGNOSTIC AGENTS

Assistant Commissioner for Patents
Washington, DC 20231
Sir:

This request for filing under Rule 53(b) is made by the following named inventor(s) (using the above-identified title): inventor(s): *MAERTENS et al.*

☒ Attached is a true copy of the prior application as originally filed including the specification, claims, Sequence Listing, Oath/Declaration and drawings (if any) and abstract (if any). No amendments (if any) referenced in the Oath or Declaration filed to complete the prior application introduced new matter.

☒ Priority is hereby claimed under 35 USC 119 based on the following foreign applications, the entire content of which is hereby incorporated by reference in this application:

Application Number	Country	Day/Month/Year/Filed
93.401 099.2	Europe	27/April/1993
93.402.019.9	Europe	05/August/1993
PCT/EP94/01323	International	27/April/1994

☐ certified copy(ies) of foreign application(s) attached or
☐ already filed on _____ in prior appln. no. _____ filed _____
☒ already filed in PCT/EP94/01323 filed April 27, 1994

☒ The prior application is assigned to N.V. INNOGENETICS S.A.
☒ Power of Attorney has been granted to Thomas E. Byrne et al. Reg. No. 32,205 of Nixon & Vanderhye P.C., 1100 N. Glebe Rd., 8th Flr, Arlington, VA 22201.
☒ Address all future communications to: Nixon & Vanderhye P.C., 1100 N. Glebe Rd., 8th Floor, Arlington, VA 22201.
☒ Please amend the specification by inserting before the first line --This is a continuation of application Serial No. 08/362,455, filed January 11, 1995, allowed, which is a 371 application of PCT/EP94/01323, filed April 27, 1994, the entire content of which is hereby incorporated by reference in this application.--
☐ Petition filed in prior application to extend its life to insure copendency.
The Examiner's attention is directed to the prior art cited in the parent application by applicant and/or Examiner for the reasons stated therein and return of an initialed copy of the attached PTO-1449 Form listing same, pursuant to MPEP §609, are requested.
☒ Please enter the attached and/or below preliminary amendment prior to calculation of filing fee:
ATTACHED
☒ The entire disclosure of the prior application above-referenced is considered as being part of the disclosure of this new application and is hereby incorporated by reference therein.

FILING FEE IS BASED ON CLAIMS AS FILED LESS ANY HEREWITH CANCELED

Basic Filing Fee					$	690.00
Total effective claims	33	- 20 (at least 20) =	3	x $ 18.00	$	54.00
Independent claims	1	- 3 (at least 3) =	0	x $ 78.00	$	0.00
If any proper multiple dependent claims now added for first time, add $250.00 (ignore improper)					$	0.00
				SUBTOTAL	$	744.00
If "small entity," then enter half (1/2) of subtotal and subtract					-$	0.00)
				SECOND SUBTOTAL	$	744.00
Assignment Recording Fee ($40.00)					$	0.00
				TOTAL FEE ENCLOSED	$	744.00

Any future submission requiring an extension of time is hereby stated to include a petition for such time extension. The Commissioner is hereby authorized to charge any deficiency in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Account No. 14-1140. A duplicate copy of this sheet is enclosed.

1100 North Glebe Road, 8th Floor
Arlington, Virginia 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100
BJS:slh

NIXON & VANDERHYE P.C.
By Atty: B.J. Sadoff, Reg. No. 36,663

Signature: [redacted]

449809

This same paragraph has been added above, with the additional indication of the status of the parent application Serial No. 08/362,455, as the Examiner has indicated in the Advisory Action dated October 13, 2004 that "There is no record of an amendment in this file dated August 15, 2000." No new matter has been added.

COPY

As explained in an Amendment dated August 25, 2003, in the related application Serial No. 09/878,281, the specification has been amended to include the heading "Brief Description of the Drawings" as suggested by the present Examiner on page 2 of the Office Action dated April 25, 2003 (Paper No. 14) in the related application Serial No. 09/878,281.

Related application Serial No. 09/878,281 has issued as U.S. Patent No. 6,762,024. A copy of the patent is attached and listed on the attached PTO 1449 Form. Return of an initialed copy of the attached PTO 1449 Form is requested. Related application Serial No. 09/878,281 (now U.S. Patent No. 6,762,024) was examined and issued by the present Examiner Martinell. The related application Serial No. 09/878,281 and the present application both claim benefit (e.g., each is a continuation of) U.S. application Serial No. 08/362,455, and also claim benefit of International Application PCT/EP94/01323.

Contrary to the Examiner's assertion in the Advisory Action dated October 13, 2004, the relationship between application Serial No. 09/878,281 and the present application is believed to be clear from the U.S. Patent Office records. Specifically, for example, the publicly available U.S. PTO PAIR page includes the following information for the above-identified information:

Parent Continuity Data				
Description	**Parent Number**	**Parent Filing or 371(c)**	**Parent Status**	**Patent Number**

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This application is a Continuation of	08/362,455	01-11-1995	Pending	-

Child Continuity Data

and the following information for the parent application Serial No. 08/362,455:

Parent Continuity Data
No Parent Continuity Data Found.
Child Continuity Data
09/638,693 filed on 08-15-2000 which is Pending claims the benefit of 08/362,455
09/873,224 filed on 06-05-2001 which is Pending claims the benefit of 08/362,455
09/878,281 filed on 06-12-2001 which is Patented claims the benefit of 08/362,455
09/899,046 filed on 07-06-2001 which is Pending claims the benefit of 08/362,455

The Examiner's comments in the Advisory Action relating to the use of the Sequence Listing from the related application are noted. Attached is a new computer readable form of the Sequence Listing, to advance prosecution. The attached paper and computer readable forms of the Sequence Listing are the same. No new matter has been added. A separate Statement to this effect is attached.

The specification has been amended to include the attached Sequence Listing as well as sequence identifiers corresponding therewith. The attached paper and computer readable copies of the Sequence Listing is the same as the paper and computer readable copies of the Sequence Listing filed in the related application Serial No. 09/878,281 on August 25, 2003. No new matter has been added.

Page 33 has been amended above to correct an inadvertent typographical error. Support for the amendment may be found in, for example, Figure 5.

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The applicants further note that page 39 has been amended as shown above to be consistent with amendments made in the related application Serial No. 09/878,281, and specifically, the applicants note that SEQ ID NOs:166, 168 etc., are mentioned on page 39 (penultimate and last bulleted point) of the description. SEQ ID NO:168 for instance has the sequence TCGF.....HRMA, as described in the Sequence Listing. Figure 5 indicates that the first amino acid T (thr) corresponds to amino acid 127 of the HCV polyprotein. Likewise, the last amino acid A (ala) of SEQ ID NO:168 corresponds to amino acid 319 of the HCV polyprotein (see Figure 5). The HCV Core protein spans positions 1-191 of the HCV polyprotein, the HCV E1 protein spans positions 192-383 of the HCV polyprotein. As SEQ ID NO:168 (and all other sequences of claim 87) starts at position 127, it will be understood to contain part of the Core protein. Hence, these sequences are to be regarded as Core/E1 proteins, as amended above. SEQ ID NO:166 is one of the sequences aligned in Figure 5 and spans amino acids 1-126 of the HCV polyprotein (MSTN.....IDTL) in accordance with SEQ ID NO:166 in Sequence Listing. As the HCV Core protein spans positions 1-191 of the HCV polyprotein, SEQ ID NO:166 will be recognized by one of ordinary skill in the art as a Core protein, as amended above.

Page 40 (1st bulleted point) of the description has been amended above with regard to SEQ ID NO:192, which the Examiner will appreciate has the sequence MSTN.....WAGW, as described in the Sequence Listing. As will be clear from the description above with regard to SEQ ID NO:166, "MSTN...." refers to the start of the HCV polyprotein Core. SEQ ID NO:192 can be allocated amino acids 1-96 of the HCV

COPY

Core polyprotein based on the sequence alignments in Figure 5. SEQ ID NO:192 is moreover one of the sequences aligned in Figure 5.

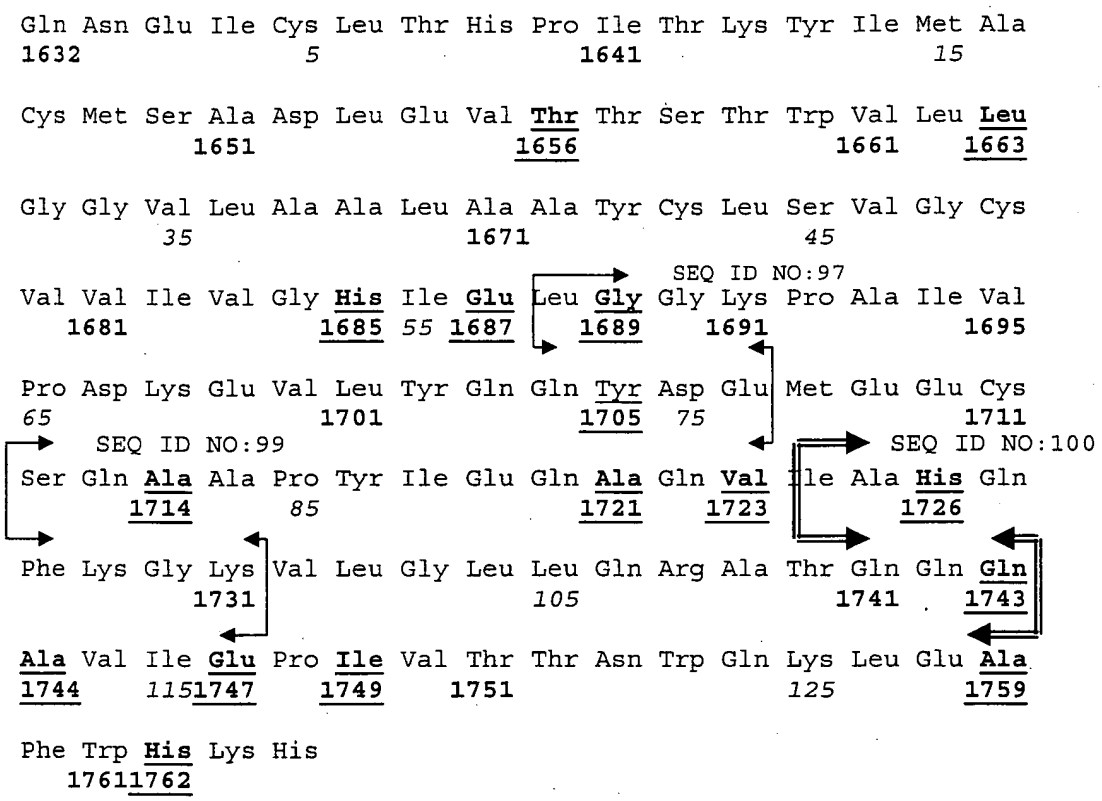
The specification has been further amended above on page 40 with regard to SEQ ID NOs:198 and 200. SEQ ID NOs:198 and 200 both cover the sequence CARTITT.....W(X/A)TY, as described in the Sequence Listing. SEQ ID NO:270 covers the sequence TITT.....WATY. SEQ ID NO:270 is one of the sequences aligned in Figure 7 (except for the first amino acid "T") and from Figure 7 one of ordinary skill in the art will appreciate that SEQ ID NO:270 spans amino acids 1284-1764 of the HCV polyprotein. SEQ ID NOs:198 and 200 both have 3 extra amino acids at their amino-terminus and thus span amino acids 1281-1764 of the HCV polyprotein. The common amino acids for the three SEQ ID NOs are 1284-1764.

No new matter has been added.

Claims 1-55, 57, 58, 60-74 and 86-91 have been canceled, without prejudice, above to advance prosecution. Upon entry of the above amendments, claims 56, 59 and 75-85 will be pending. Claim 75 has been indicated above as having been withdrawn however upon entry of the above amendments, the applicants believe claim 75 will be directed to elected subject matter such that upon entry of the above amendments, the applicants request examination of claim 75 along with claims 56, 59 and 76-85.

Specifically, as claim 56, from which claim 75 depends, is believed to include the required elements of examined claim 56. The following alignment demonstrates the relationship of the SEQ ID NO:36 and required amino acid(s) of claim 56 as compared with sequences of claim 75:

COPY



SEQ ID NO:36 of Sequence Listing

Key:
Italicized numbers = numbering according to Sequence Listing
Bold numbers = position numbers according to HCV polyprotein
Bold underlined numbers = positions recited in claims 56 and 59
Bold underlined amino acids (aa) = aa recited in claims 56 and 59

Bracketed regions highlight regions of sequences of amended claim 75 as compared with the numbering of amino acids of SEQ ID NO:36

The claims, as amended above, are submitted to read on the elected subject matter.

Reconsideration and withdrawal of the Section 112, second paragraph, rejection of claims 56, 59, 74 and 76-85 are requested as the amended claims are directed to the elected subject matter, do not specifically recite the objected to "genotype-specific amino acid", and have been amended to recite "optionally" in place of "possibly", as suggested by the Examiner on page 3, subparagraph (d) of the Office Action dated June 3, 2004.

The Examiner's continued assertion with regard to claim 74, as repeated in subparagraph (c) on page 3 of the Office Action of June 3, 2004, which refers to the comments of the Office Action of September 11, 2003, at page 3, item (c), is again not understood and clarification is requested. The Examiner is requested to appreciate that the "values" recite in claim 74, which have been canceled and are now recited in claim 56, refer to amino acid positions of the HCV polyprotein. The Examiner appears to believe the previously recitations of claim 74, and now claims 56 and 59, refer to ranges or lengths of sequences however one of ordinary skill in the art will appreciate that the amino acid numberings of positions in claims 56 and 59, and in canceled claim 74, refer, for example, to the positions as exemplified in the figures, such as Figures 7 and 11, which provide sequence alignments of previously known HCV amino acid sequences and other HCV amino acid sequences. The Examiner is further requested to note that, in contrast to the numbering of nucleotides in the HCV genome, there is only a single numbering system for amino acid of the HCV polyprotein, namely starting with methionine at position 1("M1" in terms previously recited in claim 74 and now

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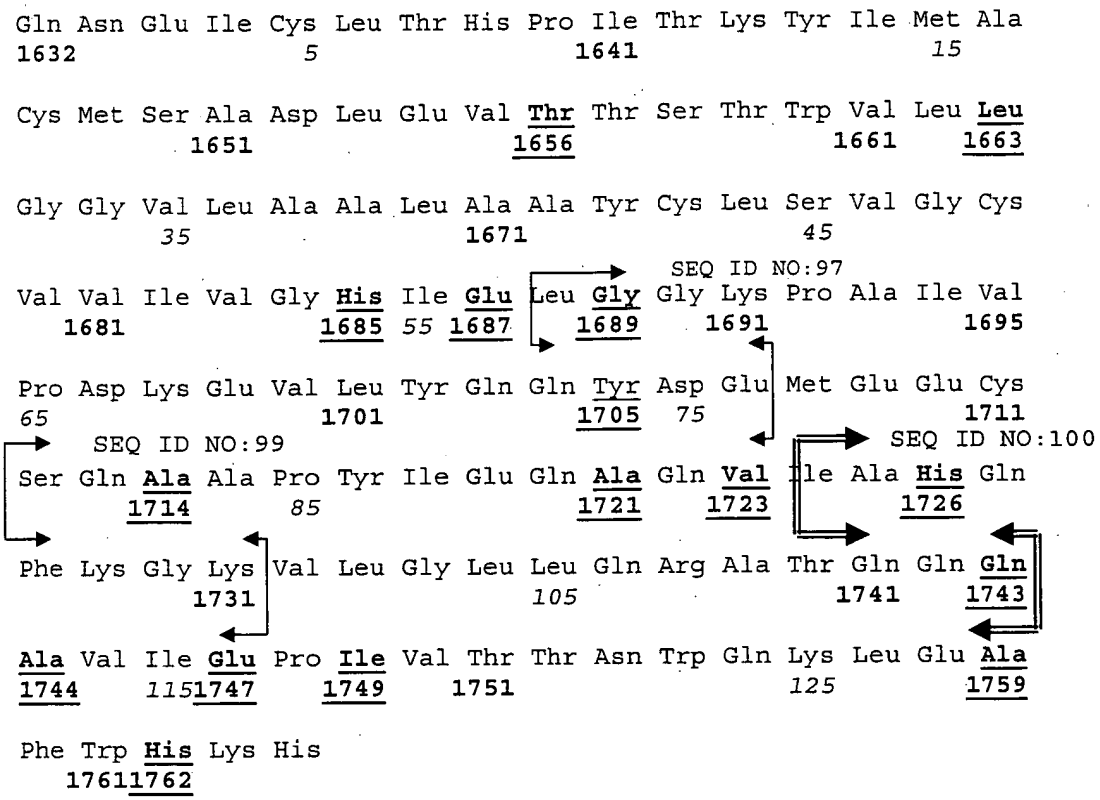
recited in claims 56 and 59), of the polyprotein. The applicants note that the relative numbering of the amino acids, may, however, vary among isolates/genotypes. See, the explanation in the third and fourth paragraphs on page 6 of the application as well as Table 1 of the page 27. The following listing and numbering of amino acids of SEQ ID NO:36 is provided for the Examiner's convenience and consideration.

COPY



SEQ ID NO:36 of Sequence Listing

Key:
Italicized numbers = numbering according to Sequence Listing
Bold numbers = position numbers according to HCV polyprotein
Bold underlined numbers = positions recited in claims 56 and 59
Bold underlined amino acids (aa) = aa recited in claims 56 and 59

Bracketed regions highlight regions of sequences of amended claim 75 as compared with the numbering of amino acids of SEQ ID NO:36

A review of the above will confirm for the Examiner that SEQ ID NO:36 is 133 residues and the "values" recited in claims 56 and 59, for example, relate to amino acid positions of the HCV polyprotein, as opposed to amino acid positions of SEQ ID NO:36. The recitation of claims 56 and 59 are submitted to be definite and will be, in the applicant's view, more readily recognizable to one of ordinary skill in the art as opposed to recitations of amino acid numbers which may reference SEQ ID NO:36.

The applicants submit, for the Examiner's convenience, that the amino acid numbers 1656, 1663, 1685, 1687, 1689, 1705, 1714, 1721, 1723, 1726, 1743, 1744, 1747, 1749, 1759 and 1762, of claims 56 and 59 correspond with amino acid positions 25, 32, 54, 56, 58, 74, 83, 90, 92, 95, 112, 113, 116, 118, 128 and 131, respectively of SEQ ID NO:36. This is clearly shown in the above depiction of SEQ ID NO:36 of the Sequence Listing. The applicants will be happy to amend claims 56 and 59 to refer to amino acid positions of SEQ ID NO:36 however the amended claims are submitted to be clear in their reference to and recitation of the numbering system used in the recitations of the claims. Claims 56, 59, 74 and 76-85, along with claim 75, are submitted to be definite and withdrawal of the Section 112, second paragraph, rejection of the same are requested.

The Section 102 rejection of claims 56, 59, 74 and 76-85 over Simmonds (WO 93/10239), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

The Examiner has rejected the noted claims over Simmonds for the following reasons:

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> "Simmonds et al. discloses peptides that are mentioned in the claims. For example, SEQ ID NO:36, positions 64-77 matches position 5-18 of the first sequence mentioned in claim 15 (page 90) of Simmonds et al and SEQ ID NO:36, positions 79-97 matches the entire second sequence mentioned in claim 15 (page 90) of Simmonds et al. Simmonds et al further teaches the use of polypeptides in the production of antibodies for use in antibody assays and also discloses the use of kits containing antibodies (*e.g.*, see pages 58-700 of Simmonds et al)." See, page 4 of the Office Action dated September 11, 2003.

The presently claimed invention is disclosed in the applicants' priority application EP 93401099.2, filed April 27, 1993, at least to the extent the Examiner alleges the invention is taught by Simmonds. The invention of the rejected claims should be accorded benefit of the priority document EP 93 401 099.2, which was filed April 27, 1993, i.e., prior to the May 27, 1993, date indicated by the Examiner as being the relevant date of the cited Simmonds reference. Consideration of the following in this regard is requested.

The following are copies of the first cover pages and pages 1, 15, 17, 19, 76, 77, 114 and 115 of the priority document EP 93401099.2, filed April 27, 1993, reproduced herein for the Examiner's convenience..

COPY

9481 1330-1 PCT/EP 94 / 01323

Europäisches Patentamt | European Patent Office | Office européen des brevets

Bescheinigung Certificate Attestation

PRIORITY DOCUMENT

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

93401099.2

Der Präsident des Europäischen Patentamts
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

H. van Bilderbeek

Den Haag, den
The Hague, 27/06/94
La Haye, le

EPA/EPO/OEB Form 2014 - 09.91

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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr. 93401099.2
Demande n°

Anmeldetag 27/04/93
Date de dépôt

Titel der Erfindung
Title of the invention
Titre de l'invention: Sequences of hepatitis C virus genotypes and their use as therapeutic and diagnostic agents

Internationale Patentklassifikation
International Patent Classification
C12N15/51, C12Q1/68, C12Q1/70, A61K39/29, G01N33/576, C07K7/04

The title of the application as originally filed reads as follows:
"New sequences of hepatitis C virus genotypes and their use as therapeutic and diagnostic agents".

COPY

2

NEW SEQUENCES OF HEPATITIS C VIRUS GENOTYPES AND THEIR USE AS THERAPEUTIC AND DIAGNOSTIC AGENTS

The invention relates to new sequences of hepatitis C virus genotypes and their use as therapeutic and diagnostic agents.

The present invention relates to new nucleotide and amino acid sequences corresponding to type-specific regions of Hepatitis C virus type 3 and the coding region of Hepatitis C virus type 4, a process for preparing them, and their use for diagnosis, prophylaxis and therapy.

The technical problem underlying the present invention is to provide new type-specific sequences of the Core, the E1, the NS3, the NS4 and the NS5 regions of HCV type 3 and type 4. These new HCV sequences are useful to diagnose the presence of type 3 and/or type 4 HCV genotypes present in a biological sample. Moreover, the availability of these new type-specific sequences can increase the overall sensitivity of HCV detection and should also prove to be useful for therapeutic purposes.

Hepatitis C viruses (HCV) have been found to be the major cause of non-A, non-B hepatitis. The sequences of cDNA clones covering the complete genome of several prototype isolates have already been determined (Kato et al., 1990; Choo et al., 1991; Okamoto et al., 1991; Okamoto et al., 1992). Comparison of these isolates shows that the variability in nucleotide sequences can be used to distinguish at least 2 different genotypes, type 1 (HCV-1 and HCV-J) and type 2 (HC-J6 and HC-J8), with an average homology of about 68%. Within each type, at least two subtypes exist (e.g. represented by HCV-1 and HCV-J), having an average homology of about 79%. HCV genomes belonging to the same subtype show average homologies of more than 90% (Okamoto et al., 1992). However, the partial nucleotide sequence of the NS5 region of the HCV-T isolates showed at most 67% homology with the previously published sequences, indicating the existence of a new type (Mori et al., 1992). Parts of the 5' untranslated region (UR), core, NS3, and NS5 regions of this type 3 have been published, further establishing the similar evolutionary distances between the 3 major genotypes and their subtypes (Chan et al., 1992).

The identification of type 3 genotypes in clinical samples can be achieved by means of PCR with type-specific primers for the NS5 region. However, the degree to which this will be successful is largely dependent on sequence variability and on the virus titer present in the serum. Therefore,

The LiPA format is completely compatible with commercially available scanning devices, thus rendering automatic interpretation of the results very reliable. All those advantages make the LiPA format liable for the use of HCV detection in a routine setting. The LiPA format should be particularly advantageous for detecting the presence of different HCV genotypes.

The present invention also relates to a method for detecting and identifying novel HCV genotypes, different from the known HCV genomes, comprising the steps of:

- determining to which HCV genotype the nucleotides present in a biological sample belong, according to the process as defined above,
- in the case of observing a sample which does not generate a hybridization pattern compatible with those defined in Table 3, sequencing the portion of the HCV genome sequence corresponding to the aberrantly hybridizing probe of the new HCV genotype to be determined.

The present invention also relates to the use of a composition as defined above, for detecting one or more genotypes of HCV present in a biological sample liable to contain them, comprising the steps of:

(i) possibly extracting sample nucleic acid,

(ii) amplifying the nucleic acid with at least one of the primers as defined above,

(iii) sequencing the amplified products

(iv) inferring the HCV genotypes present from the determined sequences by comparison to all known HCV sequences.

The present invention also relates to a composition consisting of or comprising at least one peptide or polypeptide comprising a contiguous sequence of at least 5 amino acids corresponding to an amino acid sequence encoded by at least one of the HCV genomic regions as defined above, having at least one amino acid differing from the corresponding region of HCV type 1 and/or type 2 polyprotein sequences, or mutcins thereof.

The new type 3 amino acid sequences, as deduced from the disclosed nucleotide sequences (see SEQ ID NO 1 to 42), show homologies of only 59.9 to 78% with prototype sequences of type 1 and 2 for the NS4 region, and of only 53.9 to 68.8% with prototype sequences of type 1 and 2 for the E1 region. As the NS4 region is known to contain several epitopes, for example characterized in patent application EP-A-0 489 968, and as the E1 protein is expected to be subject to immune attack as part of the viral envelope and expected to contain epitopes, the NS4 and E1 epitopes of the new type 3 and 4

vol. 15-I et II. THIEME, Stuttgart 1974.

The polypeptides of the invention can also be prepared in solid phase according to the methods described by Atherton and Shepard in their book entitled "Solid phase peptide synthesis" (IRL Press, Oxford, 1989).

The polypeptides according to this invention can be prepared by means of recombinant DNA techniques as described by Maniatis et al., Molecular Cloning: A Laboratory Manual, New York, Cold Spring Harbor Laboratory, 1982).

The present invention relates more particularly to a composition as defined above, with said polypeptide or peptide having at least one of the following amino acids in its peptidic chain:

- A157, F182, I186, H187, A190, S191 or G191, L192, W194, V202, L203, V219, I227, Q231, T237 or A237, T240, Y250, T254, S260, M271, M280, Q299, T303, L308, and L313 for the Core/E1 region, and D1556, Q1579, L1581, S1584, F1585, E1606, V1612, P1630, C1636, T1656, L1663, H1685, E1687, G1689, Y1705, A1714, A1721, V1723, H1726, R1738, Q1743, A1744, E1747, I1749, A1751, A1759 and H1762 for the NS3/NS4 region, as detected in type 3 sequences of the present invention,

- M44, Q70, A87, N106, K115, G142, I144, I178, P193, Y194, A197, M231, T232, V235, I242, S247, P249, S250, L251, V254, P257, A261, Y264, A266, G268, A280, L284, Y293, Q297, A299, and N303 in the Core/E1 region, and H1310, V1312, Q1321, P1368, V1572, N1599, F1648, P1651, V1667, T1669, A1681, A1700, Q1704, A1713, S1714, M1718, D1719, T1721, R1722, A1723, G1726, F1735, I1736, S1737, T1739, G1740, K1742, T1745, L1746, K1747, A1750, V1753, N1755, A1757, D1758, T1763, and Y1764 for the NS3/NS4 region, as detected in type 4 sequences of the present invention,

- D217, A213, A256, R294, V1677, Q1704, E1730, V1732, Q1741 and T1751 for the NS3/NS4 regions, as detected in type 3 and 4 sequences of the present invention, and with said notation being composed of a letter, unambiguously representing the amino acid by its one-letter code, and a number representing the amino acid numbering according to Kato et al., 1990 (see also Table 1 for comparison with other isolates).

For example M231 refers to a methionine at position 231. A glutamine (Q) is present at the same position 231 in type 3 isolates, whereas this position is occupied by an arginine in type 1 isolates and by a lysine (K) or asparagine (N) in type 2 isolates (see Figure 1A).

The peptide or polypeptide according to this embodiment of the

acids Q299 and T303 are unique for type 3 isolates. The type 4 isolate shows the following unique V5 sequence: RPRQHATVQN (SEQ ID NO 92), of which Q297, A299, and N303 are unique for type 4. Amino acid R294 is unique for type 3 and 4 isolates.

Consequently, the present invention also relates to a composition as defined above, wherein said peptides or polypeptides contain in their peptidic chain an amino acid sequence selected from any of the regions spanning the following positions of HCV type 3 polyproteins:

- positions 140 to 319 in the Core/E1 region, more particularly a composition wherein said polypeptide or peptide corresponds to a sequence within any of the amino acid sequences as represented in SEQ ID NO 14, 16, 18, 20, 22, 24, 26 or 28, or any other HCV amino acid sequence having a homology of more than 69%, preferably more than 70%, and most preferably more than 72% in the E1 region spanning positions 192 to 319 to any of the amino acid sequences as represented in SEQ ID NO 14, 16, 18, 20, 22, 24, 26 or 28, preferably a composition containing at least one of the following polypeptides:

LEWRNTSGLYVL (SEQ ID NO 83), VYEADDVILHA (SEQ ID NO 85), VQDGNTST (SEQ ID NO 94), VQDGNTSA (SEQ ID NO 95), VQDGNTSTCWTPV (SEQ ID NO 87), VKYVGATTAS (SEQ ID NO 96), VRYVGATTAS (SEQ ID NO 89), RPRRHQTVQT (SEQ ID NO 91), or any synthetic peptide or polypeptide containing at least 5 contiguous amino acids derived from the above-defined peptides in their peptidic chain.

- positions 1646 to 1764 in the NS3/NS4 region, more particularly a composition wherein said peptide or polypeptide corresponds to a sequence within any of the amino acid sequences as represented in SEQ ID NO 30, 32, 34, 36, 38 or 40, or any other HCV amino acid sequence having a homology of more than 76%, preferably more than 78%, most preferably more than 80% to any of the amino acid sequences as represented in SEQ ID NO 30, 32, 34, 36, 38 or 40, in the region spanning positions 1646 to 1764, preferably a composition containing at least one of the following polypeptides:

LGGKPAIVPDKEVLYQQYDE (SEQ ID NO 97),
LGGKPALVPDKEVLYQQYDE (SEQ ID NO 98),
SQAAPYIEQAQVIAHQFKEK (SEQ ID NO 99),
IAHQFKEKVLGLLQRATQQQ (SEQ ID NO 100),
IAHQFKEKILGLLQRATQQQ (SEQ ID NO 101),

or any synthetic peptide or polypeptide containing at least 5 contiguous

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(iii) ANTI-SENSE: NO

(vii) IMMEDIATE SOURCE:
(B) CLONE: BR36-20-164

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 3..401

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

```
TC CAA AAT GAA ATC TGC TTG ACA CAC CCC ATC ACA AAA TAC ATC ATG      47
   Gln Asn Glu Ile Cys Leu Thr His Pro Ile Thr Lys Tyr Ile Met
    1               5                  10                  15

GCA TGC ATG TCA GCT GAT CTG GAA GTA ACC ACC AGC ACC TGG GTT TTG    95
Ala Cys Met Ser Ala Asp Leu Glu Val Thr Thr Ser Thr Trp Val Leu
                20                  25                  30

CTT GGA GGG GTC CTC GCG GCC CTA GCG GCC TAC TGC TTG TCA GTC GGT   143
Leu Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr Cys Leu Ser Val Gly
            35                  40                  45

TGT GTT GTG ATT GTG GGT CAT ATC GAG CTG GGC GGC AAG CCG GCA ATC   191
Cys Val Val Ile Val Gly His Ile Glu Leu Gly Gly Lys Pro Ala Ile
        50                  55                  60

GTT CCA GAC AAA GAG GTG TTG TAT CAA CAA TAC GAT GAG ATG GAA GAG   239
Val Pro Asp Lys Glu Val Leu Tyr Gln Gln Tyr Asp Glu Met Glu Glu
    65                  70                  75

TGC TCA CAA GCT GCC CCA TAT ATC GAA CAA GCT CAG GTA ATA GCT CAC   287
Cys Ser Gln Ala Ala Pro Tyr Ile Glu Gln Ala Gln Val Ile Ala His
80                  85                  90                  95

CAG TTC AAG GGA AAA GTC CTT GGA TTG CTG CAG CGA GCC ACC CAA CAA   335
Gln Phe Lys Gly Lys Val Leu Gly Leu Leu Gln Arg Ala Thr Gln Gln
                100                 105                 110

CAA GCT GTC ATT GAG CCC ATA GTA ACT ACC AAC TGG CAA AAG CTT GAG   383
Gln Ala Val Ile Glu Pro Ile Val Thr Thr Asn Trp Gln Lys Leu Glu
            115                 120                 125

GCC TTT TGG CAC AAG CAT                                          401
Ala Phe Trp His Lys His
        130
```

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 133 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

```
Gln Asn Glu Ile Cys Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala
```

```
1               5                  10                  15
Cys Met Ser Ala Asp Leu Glu Val Thr Thr Ser Thr Trp Val Leu Leu
            20                  25                  30
Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr Cys Leu Ser Val Gly Cys
        35                  40                  45
Val Val Ile Val Gly His Ile Glu Leu Gly Gly Lys Pro Ala Ile Val
    50                  55                  60
Pro Asp Lys Glu Val Leu Tyr Gln Gln Tyr Asp Glu Met Glu Glu Cys
65                  70                  75                  80
Ser Gln Ala Ala Pro Tyr Ile Glu Gln Ala Gln Val Ile Ala His Gln
                85                  90                  95
Phe Lys Gly Lys Val Leu Gly Leu Leu Gln Arg Ala Thr Gln Gln Gln
            100                 105                 110
Ala Val Ile Glu Pro Ile Val Thr Thr Asn Trp Gln Lys Leu Glu Ala
        115                 120                 125
Phe Trp His Lys His
    130
```

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 401 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(vii) IMMEDIATE SOURCE:
(B) CLONE: BR36-20-166

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 3..401

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

```
TC CAA AAT GAA ATC TGC TTG ACA CAC CCC ATC ACA AAA TAC ATC ATG      47
   Gln Asn Glu Ile Cys Leu Thr His Pro Ile Thr Lys Tyr Ile Met
     1               5                  10                  15

GCA TGC ATG TCA GCT GAT CTG GAA GTA ACC ACC AGC ACC TGG GTT TTG    95
Ala Cys Met Ser Ala Asp Leu Glu Val Thr Thr Ser Thr Trp Val Leu
                20                  25                  30

CTT GGA GGG GTC CTC GCG GCC CTA GCG GCC TAC TGC TTG TCA GTC GGT   143
Leu Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr Cys Leu Ser Val Gly
            35                  40                  45
```

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(B) MAP POSITION: positions 248 to 257 of the V4 region of HCV type 3

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96:

Val Lys Tyr Val Gly Ala Thr Thr Ala Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO: 97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: BR36

(viii) POSITION IN GENOME:
(B) MAP POSITION: Positions 1688 to 1707 of HCV type 3

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97:

Leu Gly Gly Lys Pro Ala Ile Val Pro Asp Lys Glu Val Leu Tyr Gln
1 5 10 15

Gln Tyr Asp Glu
20

(2) INFORMATION FOR SEQ ID NO: 98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: BD10

(viii) POSITION IN GENOME:
(B) MAP POSITION: positions 1688 to 1707 of HCV type 3

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98:

Leu Gly Gly Lys Pro Ala Leu Val Pro Asp Lys Glu Val Leu Tyr Gln
1 5 10 15

Gln Tyr Asp Glu
20

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(2) INFORMATION FOR SEQ ID NO: 99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(viii) POSITION IN GENOME:
(B) MAP POSITION: positions 1712 to 1731

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99:

Ser Gln Ala Ala Pro Tyr Ile Glu Gln Ala Gln Val Ile Ala His Gln
1 5 10 15

Phe Lys Glu Lys
20

(2) INFORMATION FOR SEQ ID NO: 100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: BR36

(viii) POSITION IN GENOME:
(B) MAP POSITION: positions 1724 to 1743 of HCV type 1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100:

Ile Ala His Gln Phe Lys Glu Lys Val Leu Gly Leu Leu Gln Arg Ala
1 5 10 15

Thr Gln Gln Gln
20

(2) INFORMATION FOR SEQ ID NO: 101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

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The invention of the rejected claims should be accorded benefit of the priority document EP 93 401 099.2, which was filed April 27, 1993, i.e., prior to the May 27, 1993, date indicated by the Examiner as being the relevant date of the cited Simmonds reference. Specifically, the Examiner is requested to see the following portions of the priority document EP 93 401 099.2 for disclosures of the claimed invention:

"positions 1646 to 1764 in the NS3/NS4 region" and, in the same paragraph, "SEQ ID NO:36" (2nd bulleted point on page 19 and first pull paragraph of page 9 of the priority document

> Consequently, the present invention also relates to a composition as defined above, wherein said peptides or polypeptides contain in their peptidic chain an amino acid sequence selected from any of the regions spanning the following positions of HCV type 3 polyproteins:
>
> - positions 1646 to 1764 in the NS3/NS4 region, more particularly a composition wherein said peptide or polypeptide corresponds to a sequence within any of the amino acid sequences as represented in SEQ ID NO 30, 32, 34, 36, 38 or 40, or any other HCV amino acid sequence having a homology of more than 76%, preferably more than 78%, most preferably more than 80% to any of the amino acid sequences as represented in SEQ ID NO 30, 32, 34, 36, 38 or 40, in the region spanning positions 1646 to 1764, preferably a composition containing at least one of the following polypeptides:
> LGGKPAIVPDKEVLYQQYDE (SEQ ID NO 97),
> LGGKPALVPDKEVLYQQYDE (SEQ ID NO 98),
> SQAAPYIEQAQVIAHQFKEK (SEQ ID NO 99),
> IAHQFKEKVLGLLQRATQQQ (SEQ ID NO 100),
> IAHQFKEKILGLLQRATQQQ (SEQ ID NO 101).

);

the amino acid sequence of SEQ ID NO:36 is incorporated in the sequence listing (pages 76-77);

SEQ ID NOs: 97, 99 and 100 are listed at the bottom of page 19 and are also incorporated in the sequence listing (pages 114-115); and

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the following last two paragraphs on page 15 of the priority document mentions as new type 3 amino acid sequences those deduced from the nucleotide sequences in SEQ ID NO 1 to 42.

> The present invention also relates to a composition consisting of or comprising at least one peptide or polypeptide comprising a contiguous sequence of at least 5 amino acids corresponding to an amino acid sequence encoded by at least one of the HCV genomic regions as defined above, having at least one amino acid differing from the corresponding region of HCV type 1 and/or type 2 polyprotein sequences, or muteins thereof.
>
> The new type 3 amino acid sequences, as deduced from the disclosed nucleotide sequences (see SEQ ID NO 1 to 42), show homologies of only 59.9 to 78% with prototype sequences of type 1 and 2 for the NS4 region, and of only 53.9 to 68.8% with prototype sequences of type 1 and 2 for the E1 region.

In particular, SEQ ID NO:36 is the deduced from the nucleotide sequence SEQ ID NO:35 (sequence listing, page 76 of the priority document) type 3-specific amino acids in the NS3/NS4 region are recited in the following list of amino acids in the middle of page 17 of the priority document

> The present invention relates more particularly to a composition as defined above, with said polypeptide or peptide having at least one of the following amino acids in its peptidic chain:
>
> - A157, F182, I186, H187, A190, S191 or G191, L192, W194, V202, L203, V219, I227, Q231, T237 or A237, T240, Y250, T254, S260, M271, M280, Q299, T303, L308, and L313 for the Core/E1 region, and D1556, Q1579, L1581, S1584, F1585, E1606, V1612, P1630, C1636, T1656, L1663, H1685, E1687, G1689, Y1705, A1714, A1721, V1723, H1726, R1738, Q1743, A1744, E1747, I1749, A1751, A1759 and H1762 for the NS3/NS4 region, as detected in type 3 sequences of the present invention,

A complete copy of relevant pages of the priority document are reproduced above for the convenience and consideration of the Examiner.

Benefit of the priority document should be accorded the presently claimed invention and withdrawal of the Section 102 rejection of claims 56, 59, 74 and 76-85

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over Simmonds is requested as, at a minimum, the applicants priority document disclosed the presently claimed invention at least to the extent the Examiner alleges the claimed invention is disclosed in the cited Simmonds et al reference..

The Section 102 rejection of claims 56, 59, 74 and 76-85 over Chien (U.S. Patent No. 6,416,946), is similarly traversed. Withdrawal of the rejection is requested as the earliest date which appears to be applicable to the Chien reference is subsequent to the filing of the applicants' initial priority document.

The Examiner has rejected claims 56, 59, 74 and 76-85 over Chien stating the following:

> "Chien et al. discloses a polypeptide that is mentioned in the claims (*e.g.,* compare SEQ ID NO:36, positions 26-31, 33-45, and 47-53 of the instant application with matches at positions 65-70, 72-84, and 86-92, respectively of SEQ ID NO:1 of the reference. Antibody assays and kits are taught in Chien et al at columns 5-12. " See, page 4 of the Office Action dated September 11, 2003.

The applicants believe the above adequately demonstrates that the applicants priority document, which predates the cited reference, disclosed the claimed invention at least to the extent alleged to be taught by the cited art. Withdrawal of the Section 102 rejection over Chien is requested.

Moreover, the Examiner's indicated positions 26-31, 33-45 and 47-53 do not appear to be relevant to the presently claimed invention, as shon in the following alignment:

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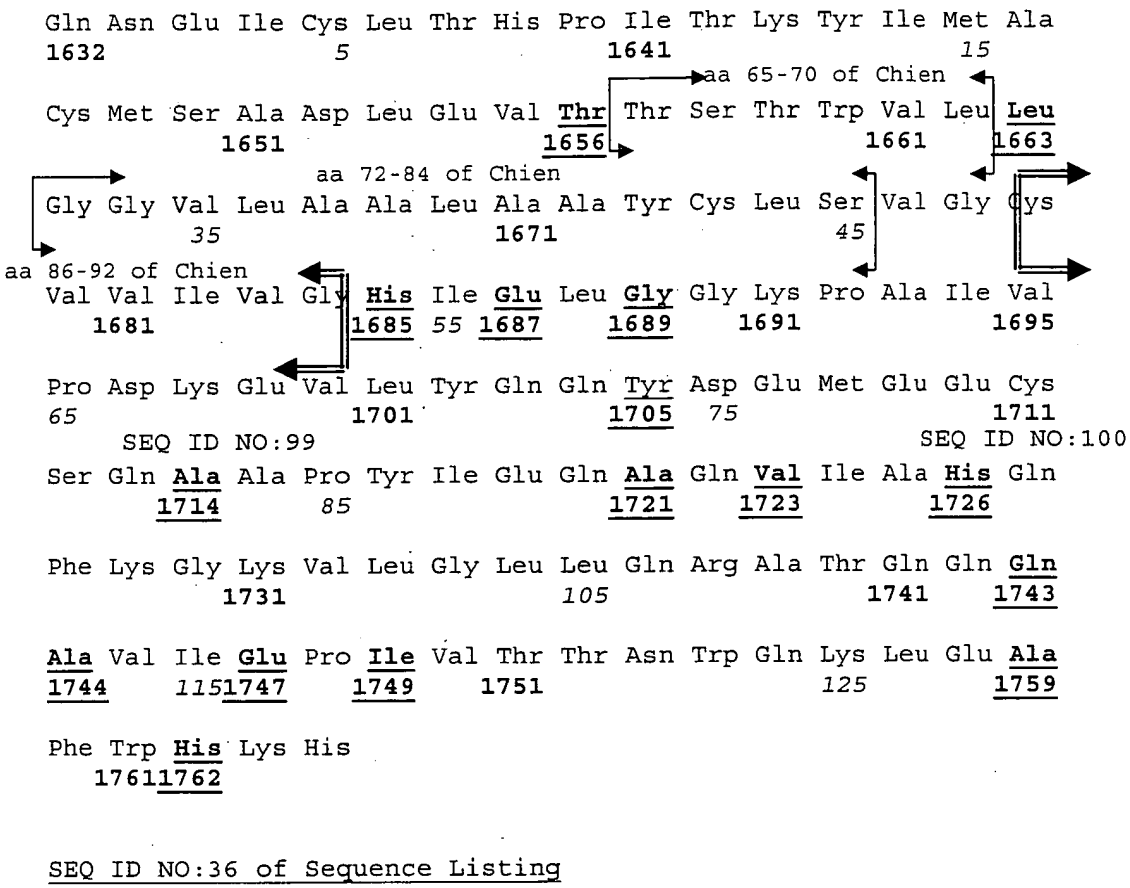

SEQ ID NO:36 of Sequence Listing

Key:
Italicized numbers = numbering according to Sequence Listing
Bold numbers = position numbers according to HCV polyprotein
Bold underlined numbers = positions recited in claims 56 and 59
Bold underlined amino acids (aa) = aa recited in claims 56 and 59

Bracketed regions of sequence shows regions of sequences SEQ ID NO:36 of present application indicated by Examiner to correspond to noted amino acids (aa) of Chien sequence.

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Reconsideration and withdrawal of the Section 102 rejection of claims 56, 59, 74 and 76-85 over Chien are requested.

The claims are submitted to be patentable and in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned if anything further is required in this regard.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____

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